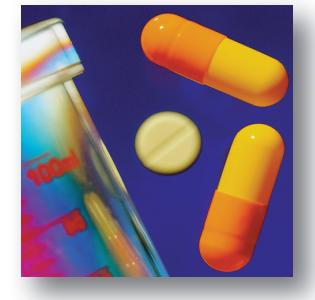

Dupilumab (Dupixent)

An Interleukin-4 Receptor Antagonist for Atopic Dermatitis

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INTRODUCTION

Atopic dermatitis (AD), also known as eczema, is a chronic, relapsing inflammatory skin disease affecting 15% to 20% of children and 1% to 3% of adults worldwide.[1] Approximately 70% of patients who experience childhood onset will have spontaneous remission.[1]

The most common symptom of AD is dry, itchy skin.[2] Other common characteristics include redness, swelling, scaly skin, crusting, and/or oozing.[2] Skin involvement and morphology are age-dependent:[3] In infants and children, AD is more common on the face, limbs, and flexural areas; in adolescents and adults, it is more common on the hands and feet.[3]

Various causes and risk factors are implicated in AD, including genetics. Mutations of the filaggrin gene (FLG) are commonly associated with dermatological diseases; nearly half of FLG mutation carriers have AD.[4] This gene encodes an epidermal protein that is expressed in the outer layers of the epidermis.[4] Any variation in this gene can cause failure in the barrier function of the skin.[4]

Pollutants, such as carbon monoxide, whether inhaled, ingested, or absorbed through skin, may influence the immune system, particularly during development.[5] Contact allergens and skin irritants can also exacerbate AD.[5]

AD is a step in the well-known "atopic march," the progression of atopic or allergic diseases that also includes food allergies, allergic rhinitis, and asthma.[1] Childhood onset of AD often means the child may develop one of the other diseases later in life.[1] Patients with AD are at a higher risk for skin infections with *Staphylococcus aureus* due to reduced antimicrobial peptide expression in the skin.[6] This susceptibility to infection is intensified by the itch–scratch cycle.[2] Immune cells in the deeper layers of the skin send inflammatory signals to the surface, causing the itchy rash.[2] Scratching breaks the outer layer of skin, allowing germs, viruses, and allergens to enter.[2]

AD can be categorized as inactive (asymptomatic) or active.[5] Recommended therapy for the inactive state focuses on emollients (moisturizers), which form an occlusive layer and prevent the skin from drying out.[3,7] Thick creams, such as Eucerin and Cetaphil, or ointments, such as Aquaphor and Vaseline, are most efficacious in AD.[7]

When the disease becomes active, patients experience flare-ups, characterized by excessive dryness, itching, redness, and swelling.[8] To prevent flare-ups, it is most important to avoid triggers, such

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Table 1 Potency of Topical Steroids[10]

Drugs	Dosage Forms Available
Class 1: Super-High Potency	
Betamethasone dipropionate, augmented 0.05%	Gel, lotion, ointment
Clobetasol propionate 0.05%	Cream, foam aerosol, gel, lotion, ointment, shampoo, solution
Fluocinonide 0.1%	Cream
Halobetasol propionate 0.05%	Cream, lotion, ointment
Class 2: High Potency	
Amcinonide 0.1%	Ointment
Betamethasone dipropionate 0.05%	Ointment
Desoximetasone 0.25%	Cream, gel, ointment
Diflorasone diacetate 0.05%	Cream, ointment
Fluocinonide 0.05%	Cream, gel, ointment, solution
Halcinonide 0.1%	Cream, ointment
Class 3: Upper Medium Potency	
Amcinonide 0.1%	Cream, lotion
Betamethasone dipropionate 0.05%	Cream
Betamethasone valerate 0.12%, 0.1%	Foam, ointment
Desoximetasone 0.05%	Cream
Diflorasone diacetate 0.05%	Cream
Fluocinonide 0.05%	Cream
Fluticasone propionate 0.005%	Ointment
Mometasone furoate 0.1%	Ointment
Triamcinolone acetonide	Cream, ointment

table continues

Table 1 Potency of Topical Steroids[10] (continued)	
Drugs	**Dosage Forms Available**
Class 4: Medium Potency	
Betamethasone dipropionate 0.05%	Spray
Fluocinolone acetonide 0.025%	Ointment
Flurandrenolide 0.05%	Ointment
Hydrocortisone 0.2%	Ointment
Mometasone furoate 0.1%	Cream, lotion, solution
Triamcinolone acetonide 0.1%	Aerosol spray, cream, ointment
Class 5: Lower Medium Potency	
Betamethasone dipropionate 0.05%	Lotion
Betamethasone valerate 0.1%	Cream
Desonide 0.05%	Gel, ointment
Fluocinolone acetonide 0.025%	Cream
Flurandrenolide 0.05%	Cream, lotion
Fluticasone propionate 0.05%	Cream, lotion
Hydrocortisone butyrate 0.1%	Cream, lotion, ointment, solution
Hydrocortisone probutate 0.1%	Cream
Hydrocortisone valerate 0.2%	Cream
Prednicarbate 0.1%	Cream, ointment
Triamcinolone acetonide 0.1%, 0.025%	Lotion, ointment
Class 6: Low Potency	
Alclometasone dipropionate 0.05%	Cream, ointment
Betamethasone valerate 0.1%	Lotion
Desonide 0.05%	Foam, cream, lotion
Fluocinolone acetonide 0.01%	Cream, oil, shampoo, solution
Triamcinolone acetonide 0.025%	Cream, lotion
Class 7: Least Potent	
Hydrocortisone 1%, 2.5%	Cream, lotion, ointment

as irritants, contact allergens, and inhaled allergens.[8] Current first-line treatments for AD flare-ups are topical steroids, followed by topical calcineurin inhibitors.[3] The choice of topical steroid depends on the age of the patient, site of application, and distribution and severity of disease.

The topical steroids are categorized into 7 classes according to their potency and vasoconstrictive properties, with Class 1 being the most potent and Class 7 being the least potent (Table 1).[9,10] All topical steroids can be applied once or twice a day but should not be used for more than 4 weeks.[11] Topical calcineurin inhibitors, tacrolimus and pimecrolimus, should be applied twice a day.[12,13] Both have age restrictions based on their potency. Tacrolimus 0.1% ointment can be used only in children older than 16 years of age and adults, while tacrolimus 0.03% ointment and pimecrolimus 1% ointment can be used in children older than 2 years of age and adults.[12,13]

The topical calcineurin inhibitors cause less skin atrophy compared with the topical steroids; however, they do cause more burning and stinging and are accompanied by a boxed warning of an increased risk of lymphomas with long-term use.[3] Systemic agents, such as oral corticosteroids, cyclosporine, azathioprine, and mycophenolate, may also be used for severe, refractory AD.[8]

In 2017, the FDA approved injectable dupilumab (Dupixent), which is indicated for the treatment of adults with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids.[14] It is produced by recombinant DNA technology in Chinese hamster ovary cell suspension culture and has a molecular weight of 147 kDa.[14]

PHARMACOLOGY

Mechanism of Action[14]

Dupilumab is an interleukin-4 (IL-4) receptor alpha antagonist. It is a human monoclonal antibody of the immunoglobulin G4 subclass that inhibits IL-4 and interleukin-13 (IL-13) signaling by specifically binding to the IL-4 receptor alpha subunit, which is shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the type 1 receptor and both IL-4 and IL-13 signaling via the type 2 receptor. By blocking the IL-4R alpha subunit, dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin E.

Pharmacodynamics[14]

The relationship among the pharmacodynamic activity and mechanisms by which dupilumab exerts its clinical effects is unknown. However, serum levels of IL-4 and IL-13 were increased following dupilumab treatment, which is consistent with receptor blockade.

Pharmacokinetics[14]

Following an initial subcutaneous dose of 600 mg, dupilumab reached a peak maximum concentration of 70.1 ± 24.1 mcg/mL by approximately one week after the dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg as an initial dose and 300 mg either every other week or weekly (twice the recommended frequency).

Across clinical trials, the mean steady-state trough concentrations ranged from 73.3 ± 40.0 mcg/mL to 79.9 ± 41.4 mcg/mL for 300 mg administered every 2 weeks and from 173 ± 75.9 mcg/mL to 193 ± 77.0 mcg/mL for 300 mg administered weekly.[14]

Following a subcutaneous dose, the bioavailability of dupilumab is about 64%.

Table 2 Outcome Measures[14,15,16]

	Dupilumab Monotherapy				Dupilumab + Topical Steroids	
	Trial 1 (SOLO 1)		Trial 2 (SOLO 2)		Trial 3	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo + TCS	Dupilumab + TCS
IGA score 0 or 1	10%	38%	9%	36%	12%	39%
EASI-75*	15%	51%	12%	44%	69%	23%
Peak pruritus numerical-rating scale (NRS) score (≥ 4-point improvement)	12%	41%	36%	10%	20%	59%

EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; TCS = topical corticosteroids.

*An improvement from baseline of at least 75% on the Eczema Area and Severity Index.

The estimated total volume of distribution is about 4.8 ± 1.3 L.[14] The metabolic pathway of dupilumab has not been characterized. Dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous immunoglobulin G because it is a human monoclonal immunoglobulin G4 antibody.[14]

CLINICAL TRIALS

Three randomized, double-blind, placebo-controlled trials enrolled 2,119 subjects 18 years of age and older with moderate-to-severe AD not adequately controlled by topical glucocorticoids and calcineurin inhibitors.[14] Dupilumab was evaluated as monotherapy in two 16-week trials (SOLO 1 and SOLO 2), and in combination with topical corticosteroids (TCS) in one 52-week trial (LIBERTY AD CHRONOS).[14] Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥ 3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥ 10%.[14]

The primary endpoint of all three studies was assessed at 16 weeks and included a change from baseline of subjects with an IGA of 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included subjects with EASI-75 score (75% improvement in EASI score from baseline) and at least a 4-point improvement from baseline in the peak pruritus numerical-rating scale score.[14]

SOLO 1 and SOLO 2 confirmed and expanded the results of previous trials. Patients received dupilumab 300-mg injections, placebo injections, or alternative dupilumab and placebo injections for 16 weeks.[15] Significantly more patients receiving dupilumab met the primary outcome, compared with patients receiving placebo (P<0.001). In addition, significantly more patients in the dupilumab group reported an improvement of at least 75% on the EASI score, compared with those in the placebo group (P < 0.001).[15] Patients in the dupilumab group also reported significantly reduced symptoms of AD and its effect on sleep, symptoms of anxiety and depression, and quality of life (Table 2).[15]

In the dupilumab + TCS trial, 53% of IGA 0 or 1 responders at Week 16 remained responders at Week 52 and 24% of IGA 0 or 1 nonresponders at Week 16 later responded to treatment at Week 52.[14,16] In addition, 69% and 65% of patients treated with dupilumab + TCS achieved EASI-75 at 16 weeks and 52 weeks, respectively, versus 23% and 22% with placebo + TCS (P ≤ 0.001).[14,16] In the CHRONOS study, 40% of patients treated with dupilumab + TCS achieved EASI-90 at 16 weeks, versus 11% with placebo (P ≤0.001).[16]

SAFETY

Warnings, Precautions, and Contraindications[14]

Conjunctivitis and keratitis occurred more frequently in patients receiving dupilumab. Keratitis may be more likely when dupilumab and topical corticosteroids are used together. Patients should report new onset or worsening eye symptoms.

The safety and efficacy of dupilumab have not been established in the treatment of asthma. Patients with comorbid asthma should not adjust or stop their asthma treatment without consulting their physician.

The use of dupilumab is contraindicated in patients with known hypersensitivity to dupilumab or any of its excipients.

Adverse Reactions[14]

The most common adverse events are injection-site reactions, conjunctivitis, blepharitis, keratitis, eye pruritus, oral herpes or other herpes simplex virus infections, and dry eyes.

Drug Interactions[14]

Patients being treated with dupilumab should avoid the use of live vaccines.

Monitor therapy with concomitant use of dupilumab and cytochrome (CYP) 450 substrates (i.e., warfarin, cyclosporine). Increased levels of certain cytokines, including IL-4 and IL-13, can alter the formation of CYP450 enzymes.

Use in Specific Populations

Pregnancy and Lactation[14]

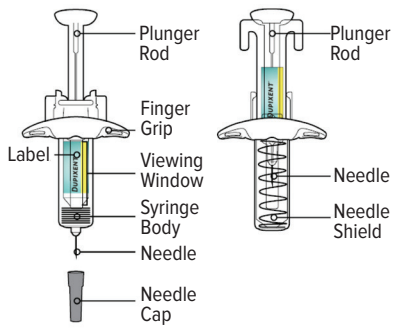
No data are available on the use of dupilumab in pregnant women. Human immunoglobulin G antibodies are known to cross the placental barrier; therefore, dupilumab may be transmitted from the mother to the fetus.

There are also no available data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human immunoglobulin G is known to be present in human milk.

Pediatric and Geriatric Use[14]

There are no available data on the safety and efficacy of dupilumab in pediatric patients. Although no differences in safety and efficacy were observed between older and younger patients in clinical trials, the number of patients 65 years of age and older is not sufficient to determine whether they respond differ-

Figure 1 Dupilumab Device[14]



ently than younger patients. However, based on the studies, no dose adjustments are recommended for this population.

DOSAGE AND ADMINISTRATION[14]

Dupilumab is available as a 300 mg/2 mL solution in a single-dose prefilled syringe with or without a needle shield (Figure 1). The recommended initial dose is 600 mg (two 300-mg injections in different injection sites), followed by 300 mg every other week. Topical calcineurin inhibitors, such as tacrolimus or pimecrolimus, may be used but should be reserved only for problem areas, such as the face, neck, intertriginous areas, and genital areas.[14]

Dupilumab is administered by subcutaneous injection to the thigh or abdomen, avoiding two inches around the navel. If a caregiver administers the injection, it can also be given on the upper arm. Do not administer the drug into skin that is tender, bruised, damaged, or scarred. Rotate the injection site with each injection.[14]

Before injecting, remove the prefilled syringe from the refrigerator and allow it to reach room temperature for 45 minutes. Inspect dupilumab for any particulate matter and discoloration prior to injecting.[14]

Dupilumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution. In addition to dupilumab, each syringe also contains L-arginine hydrochloride (10.5 mg), L-histidine (6.2 mg), polysorbate 80 (4 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.[14]

Patients who miss a dose should administer it within seven days and resume the original schedule. If the dose is not administered within 7 days, the patient must wait until the next dose on the original schedule.[14]

STORAGE[14]

Dupilumab should be stored refrigerated (2–8° C) in the original carton to protect it from light. Prefilled syringes may be kept at room temperature (25° C) for a maximum of 14 days. Do not store above 25° C. After removal from the refrigerator, the medication must be used within 14 days or discarded. Any unused portion should also be discarded. Do not expose the syringe to heat or direct sunlight, do not freeze, and do not shake.[14]

P&T COMMITTEE CONSIDERATIONS

Because there are limited treatment options for moderate-to-severe AD, dupilumab may be beneficial for patients who are inadequately controlled on topical steroids and/or calcineurin inhibitors.[15,16] Dupilumab treatment resulted in highly reproducible improvements for all clinical endpoints when administered as monotherapy, as well as in combination with topical corticosteroids.[15,16] Studies have shown that dupilumab can reduce the severity of the disease and symptoms such as pruritus.[15] It has also been proven to reduce symptoms of anxiety and depression and to improve quality of life.[15] It is considered a specialty product and the average wholesale price (AWP) for 1 box of 2 prefilled syringes (300 mg/2 mL) is $3,517.85.[17] Although dupilumab may cause mild injection-site reactions, patients in placebo groups had higher rates of skin infections and dropped out more often.[18]

CONCLUSION

Dupilumab is the only FDA-approved medication for moderate-to-severe atopic dermatitis that is administered weekly.[14] This may greatly increase patient compliance, and thus improve symptoms. Dupilumab treatment was not only associated with improvement in skin lesions, but also with rapid reductions in pruritus and other symptoms that place a burden on patients with atopic dermatitis.[18]

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